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ON ADRENALIN GLYCOSURIA AND CERTAIN RELATIONS BETWEEN THE ADRENAL GLANDS AND CARBOHYDRATE METABOLISM.

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THE adrenal gland was for the first time brought into relation with glycosuria by F. Blum,[1] of Frankfort, who in September, 1901, published observations showing that extracts of the adrenal glands of sheep are capable of inducing a slight or moderate grade of glycosuria when injected subcutaneously into dogs and rabbits. The results of Blum were confirmed in Europe, and led in this country to experiments with Takamine's adrenalin chloride and Abel's adrenalin which have extended our information as to the glycosuria following the administration of preparations made from the adrenals. Herter and Richards[2] found that the intraperitoneal injection of solutions of adrenalin chloride is followed almost regularly by the presence of large percentages of sugar in the urine, and the present writers made a study of some of the conditions under which adrenalin glycosuria occurs.[1] In this paper it is desired to offer a summary of the more important observations that have now been made, in the belief that they are of interest as throwing new light on the physiology of carbohydrate metabolism.

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[1] Ueber Nebennierendiabetes, Deutsches Archiv für klin. Medicin, Bd. lxxi.

[2] Medical News, February 1, 1902.

General Description of Experimental Adrenalin Glycosuria. The intensity and duration of adrenalin glycosuria depend in part on the mode of administration, in part on the size of the dose. Subcutaneous injections yield less sugar than intravenous or intraperitoneal injections. Direct applications to the surface of the pancreas usually cause considerable excretion of sugar, even when the quantity of adrenalin used is small (say 1 c.c. solution of adrenalin chloride 1 : 1000). The slightest glycosurias in proportion to the dose have come from the use of adrenalin chloride by the mouth. Dogs of medium size may receive 10 to 20 c.c. of the commonly used adrenalin chloride solution (1 : 1000) without developing glycosuria; larger doses may be followed by a moderate or considerable glycosuria. This relative inertness of the substance when given by the mouth has a certain practical importance, and is readily explained. Adrenalin is very easily oxidized, and quickly loses both its blood-pressure-raising property and its ability to induce glycosuria. When introduced into the stomach the gastric epithelial cells have an opportunity to destroy a considerable portion of the active substance before it is absorbed. It thus loses a large part of its efficacy in raising the blood pressure. It is preferable to give adrenalin subcutaneously to giving it by the stomach, for, in addition to securing greater precision and economy in dosage, this method has the advantage of avoiding any ill effects upon the stomach. We have never known the usual dose for subcutaneous use

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[1] Table Showing Effect of Intraperitoneal Injection of Adrenalin of Dilution 1 : 1000.

Weight of dog.	Amount of solution used.	First catheterization after	Sugar.	Second catheterization after	Sugar.	
18.6 kilo.	9 c.c.	1 hour.	5.0 per ct.			
21 "	10 "	....	1.0 "			
8.2 "	7 "	1 hour.	10.0 "			
11.3 "	10 "	1 "	5.3 "			
10.9 "	10 "	30 min.	5.0 "	1 hr. 30 min.	6.5 per ct.	
13.2 "	11.5 "	2 hr. 30 min.	5.0 "	3 " 10 "	7.33 "	
10 "	5 "	40 min.	6.11 "	2 " 20 "	11.5 "	
5 "	2 "	4 hours.	3.75 "			
6.8 "	10 "	....	4.8 "			
8.2 "	5 "	....	1.25 "			
7.3 "	5 "	....	2.7 "			
7.3 "	10 "	1 hr. 25 min.	2.0 "	6 hr. 30 min.	4.2 per ct.	Abel's adrenalin.
6.4 "	10 "	1 " 10 "	7.15 "	....	......	" "

(0.3 to 1.2 c.c.) to occasion glycosuria, even when repeated at intervals of three or four hours.

The degree and duration of the glycosuria vary widely in different animals, and sometimes in the same animals at different times. Intraperitoneal injections of 5 c.c. of adrenalin chloride in normal dogs of medium size (8 to 15 kilos) almost without exception cause the appearance (within one or two hours) of a glycosuria, with from 3 to 10 per cent. of sugar in the urine. The duration of the glycosuria following a single dose is seldom longer than thirty hours. During this time there is a total excretion of glucose which does not commonly exceed 2 or 3 grammes. The amount of sugar which appears during and after frequently repeated doses of adrenalin may greatly exceed these amounts. For example, this is well shown in the following experiment, in which the pancreas was repeatedly painted with adrenalin:

Experiment. Normal dog; weight, 13.6 kilos; well nourished. Meat diet. Bladder emptied; urine normal. Lacteals found distended. Pancreas divided into two nearly equal parts. Adjoining duodenum also cut through transversely. Between 10.45 A.M. and 9.25 P.M. head end of the pancreas painted ten times with 1 c.c. adrenalin chloride solution (1 : 1000). Slightly under ether throughout the entire experiment.

Urine,	first	catheterization	12.35	P.M.,	70 c.c.,	7.25	per cent.	sugar.
"	second	"	2.15	"	60 c.c.,	14.3	"	"
"	third	"	3.15	"	48 c.c.,	12.5	"	"
"	fourth	"	4.30	"	25 c.c.,	9.75	"	"
"	fifth	"	5.50	"	14 c.c.,	6.0	"	"
"	sixth	"	7.00	"	10 c.c.,	2.22	"	"
"	seventh	"	8.00	"	6 c.c.,	1.82	"	"
"	eighth	"	9.00	"	7 c.c.,	1.4	"	"
"	ninth	"	10.15	"	4.5 c.c.,	0.83	"	"

The total quantity of sugar excreted during this experiment was 23.4 grammes (estimated as glucose). The observation is instructive not merely in showing how high a grade of glycosuria may be caused by the action of adrenalin, but also as indicating how small a quantity of adrenalin is capable of calling forth so great an amount of sugar. The amount of adrenalin substance employed in this experiment was approximately 0.01 gramme. We do not know of any form of experimental glycosuria in which such pronounced effects can be obtained with so small a quantity of toxic material.

The susceptibility of different dogs to adrenalin varies considerably so far as glycosuria is concerned. One sometimes finds animals which do not show any glycosuria whatever, even after one or more applications to the pancreas.[1] The differences noted appear to be connected with the state of nutrition, and especially with the quantity of glycogen which is stored in the organism. It appears doubtful, however, if these differences in susceptibility can be accounted for wholly in this way. It seems to us that there are other factors of which the nature is unknown.

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[1] Many of our animals showed themselves insusceptible to the action of piperidin in causing glycosuria, while others excreted very large quantities of sugar. This difference appeared to be largely independent of the size of the dose applied to the pancreas.

In adrenalin glycosuria the sugar of the blood is regularly increased but falls rapidly with the decline in the sugar of the urine, and after a time may drop below the original normal level. In respect to the increase of blood sugar adrenalin glycosuria resembles the majority of cases of human diabetes, and differs from the experimental glycosuria after phloridzin, where the sugar-content of the blood is commonly lower than normal. The volume of the urine in adrenalin glycosuria is usually distinctly increased. The presence of diacetic acid or oxybutyric acid has not been observed. The occurrence of glycosuria from adrenalin is wholly independent of any change in the general blood pressure, as was shown in experiments where sugar occurred in the urine in spite of a marked fall in carotid blood pressure from nitroglycerin.

PHYSIOLOGICAL CHARACTERS OF ADRENALIN GLYCOSURIA. One of the first questions that arises relates to the origin of the sugar which appears in the urine. This sugar might be thought of as coming either from an increased conversion of hepatic glycogen or from a diminished combustion of sugar. In favor of the former view are two facts—first, the decline in the glycogen store of the liver during adrenalin glycosuria; and, secondly, the increased sugar-content of the blood of the hepatic vein as compared with the blood of the portal vein. The following table gives three typical observations made by Dr. Richards upon the sugar of the blood of the femoral artery, portal vein, and hepatic vein, before and after treatment of the pancreas with adrenalin. The collections of blood were made simultaneously by means of specially designed canulæ.

These figures call for little comment. In two of the three observations the sugar of the blood of the femoral artery, portal vein, and hepatic vein showed a fairly close correspondence before the application of adrenalin. In the third case the blood sugar of the hepatic vein was considerably lower than that of the blood of the portal vein. In all three cases the percentage of blood sugar of the hepatic vein rose quickly to a point in excess of the percentage in the portal vein, and remained so during the subsequent observations. It is safe to infer that this behavior of the blood sugar is referable to the increased production of sugar within the liver.

TABLE SHOWING PERCENTAGE OF SUGAR IN BLOOD BEFORE AND AFTER TREATMENT OF PANCREAS WITH ADRENALIN.

Weight of dog.	Starved.	Blood drawn at	Pancreas painted at	Sugar in blood from		
				Femoral artery.	Portal vein.	Hepatic vein.
8.2 kilo.	48 hours.	3.50 P.M.	....	0.142 per ct.	0.148 per ct.	0.143 per ct.
		....	4.04 P.M.			
		4.08 P.M.		0.191 "	0.151 "	
		4.21 "		0.179 "	0.154 "	0.177 "
		5.07 "		0.132 "	0.107 "	0.130 "
9.2 kilo.	24 hours.	4.23 P.M.	....	0.160 per ct.	0.165 per ct.	0.164 per ct.
		....	4.39 P.M.			
		4.49 P.M.		0.247 "	0.197 "	0.284 "
		5.20 "		0.322 "	0.245 "	0.346 "
7.8 kilo.	20 hours.	4.21 P.M.	....	0.159 per ct.	0.169 per ct.	0.136 per ct.
		....	4.40 P.M.			
		4.44 P.M.		0.187 "	0.167 "	0.201 "
		5.06 "		0.215 "	0.187 "	0.252 "
		4.46 "		0.208 "	0.207 "	0.209 "

In what way adrenalin occasions an excessive conversion of glycogen into sugar is still undecided, but there are some experimental observations that have to be considered in any attempt to form a judgment on this question. One of these is that applications of small amounts of adrenalin to the surface of the pancreas or injections into its substance have given rise to a more pronounced glycosuria than similar procedures in the case of the brain, liver, spleen, or kidney.[1] This suggests that in the production of glycosuria adrenalin acts especially, if not exclusively, upon the cells of the pancreas; but it has been impossible to prove that the action of adrenalin depends wholly on the presence of the pancreas, for total extirpation of this gland is quickly followed by an excretion of sugar.[2] Another difficulty arises from the fact that since adrenalin acts when introduced into the circulation, the substance may find its way to other organs when applied to the surface of the pancreas. If, however, it could be shown that there are substances which are capable of inducing glycosuria when painted on the pancreas, but do not cause it when introduced into the circulation or into the brain, spleen, or liver, we should have strong evidence that the substances in question when applied to the pancreas act on this organ only. A substance of this nature is potassium cyanide. The action of this poison in its relation to glycosuria is illustrated by the following tables:

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[1] No observations of this kind have as yet been made upon the adrenal bodies.

[2] It is possible that some information could be obtained after total extirpation of the pancreas by making intraperitoneal injections of adrenalin when the quantity of sugar excreted from hour to hour is small and fairly constant.

TABLE SHOWING EFFECT OF APPLYING POTASSIUM CYANIDE SOLUTIONS TO PANCREAS.[1]

Weight of dog.	How applied to pancreas.	Amount of solution used.	Strength of solution.	Duration of application.	First catheterization after	Volume of urine.	Sugar.	
......	Painted.	2 c.c.	$\frac{N}{1000}$	......	1 hour.	——	2.1 %	
4.5 kilo.	Painted.	3 "	"	30 min.	1 h. 40 m.	2 c.c.	'strong'	
6.8 "	Painted and injected.	2 "	"	10 "	1 hour.	9 "	0	
9.5 "	Painted and injected.	2 "	"	......	30 min.	......	6.0 %	Applicati'n to tail of pancreas.
7.2 "	Painted.	1.5 "	"	13 min.	2 hours.	5 "	1.5 %	
9.1 "	Injected.	3 "	"	......	2 "	4 "	trace.	
11.8 "	Painted and injected.	3 "	"	10 min.	1 hour.	9 "	0	
10.4 "	Injected.	3 "	"	10 "	2 h. 45 m.	65 "	0.25 %	Applicati'n to head of pancreas.
6.8 "	Painted and injected.	2 "	"	10 "	2 hours.	8 "	trace.	
5.4 "	Painted and injected.	2 "	"	......	4 h. 45 m.	7 "	trace.	

TABLE SHOWING EFFECT OF INTRODUCING POTASSIUM CYANIDE SOLUTIONS INTO A MESENTERIC VEIN OR INTO THE FEMORAL VEIN.

Weight of dog.	Where injected.	Amount of solution injected.	Strength of solution.	Duration of injection.	First catheterization after	Volume of urine.	Sugar.
9.1 kilo.	Into mesenteric vein.	3 c.c.	$\frac{N}{1000}$	——	1 h. 10 m.	——	0
10.9 "	" "	6 "	"	——	——	——	0
6.8 "	" "	10 "	"	2 min.	2 hours.	13 c.c.	0
4.5 "	" "	14 "	"	2 "	2 h. 15 m.	35 "	0
8.2 "	" "	250 "	"	60 "	2 h. 10 m.	0	
7.7 "	" "	85 "	"	——	2 h. 15 m.	23 c.c.	0
7.3 "	Into femoral vein.	5 "	"	25 min.	2 hours.	5.5 "	0
7.7 "	" "	3 "	"	30 "	2 hours.	12 "	0
9.1 "	" "	6 "	"	15 "	1 h. 30 m.	25 "	0
7.3 "	" "	200 "	$\frac{N}{100}$	——	——	——	0
6.4 "	" "	200 "	$\frac{N}{750}$	60 min.	30 min.	4 c.c.	0

It is apparent that a dilute solution $\left(\frac{N}{1000}\right)$ of potassium cyanide when applied to the surface of the pancreas is capable of inducing a glycosuria of slight degree, which is dependent not on the transportation of this poison to some distant part by means of the blood, but on its direct influence on the cells of the gland. There is, of course, no evidence that there are not other cells in the body which react to hydrocyanic acid in such a way as to provoke glycosuria; but experiments made upon the cerebral cortex, the liver, the spleen, and the decapsulated kidney gave negative results. These various experiments with potassium cyanide, in connection with the observed sensitiveness of the pancreas to local applications of adrenalin, point to the pancreas as the part chiefly concerned in the production of adrenalin glycosuria, although here, again, there is no proof that some cells other than those of the pancreas do not possess a similar sensitiveness.

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[1] The animals were in almost every instance fed on lean meat.

How the application of adrenalin to the pancreas initiates those hepatic changes which result in glycosuria is not yet clear. We at one time thought it possible that during the glycosuria something leaves the pancreas by the pancreaticoduodenal vein which stimulates the conversion of glycogen into sugar. Experiments designed to test this idea did not give it any support. At present it appears much more likely that the glycogenetic function of the liver is stimulated through the mediation of the sympathetic nervous system. No direct investigation of this phase of the subject has yet been made.

As to the way adrenalin acts on the cells of the pancreas there is no positive information, although there are two considerations which led us to conclude that the disturbance of function is of a kind that involves impaired oxidation within the pancreatic cells. One of these is that hydrocyanic acid has the property of interfering with the capacity of cells to appropriate oxygen, as was shown conclusively by the work of Geppert. It is conceivable that hydrocyanic acid has other properties which contribute to render it poisonous, but the interference with oxidation seems to sufficiently account for its powerful toxic action. It is therefore reasonable to assume that the ability of potassium cyanide to cause glycosuria is due to interference with the appropriation of oxygen by the pancreatic cells. It is possible that this disturbance in oxidation makes itself felt in an action upon the nerve-endings in the pancreas, resulting in the hepatic overaction already mentioned in speaking of adrenalin glycosuria.

What we know about the action of hydrocyanic acid led us to inquire whether there are not other poisons that have a similar action upon cells in respect to interference with intracellular oxidations. It was found that there are many substances which lead to glycosuria when applied directly to the pancreas. Comparing these with respect to their ability to oxidize or reduce, it was found that substances which exert a reducing action are more likely to induce glycosuria than those which have an oxidizing action. It must be admitted, however, that it has been possible to experiment with only a relatively small number of oxidizing and reducing agents, and that a wider experience may not sustain the generalization that the property of inducing glycosuria belongs much more to reducing than to oxidizing substances. On the other hand, the results obtained up to the present cannot be ignored. It is impracticable to give these results in detail here, but some facts regarding them should be mentioned. Thus it was found that substances which reduce Fehling's solution occurred in the urine after the application of the following poisons to the pancreas: sulphurous acid, sulphuretted hydrogen, carbon monoxide, benzyl alcohol, and pyrogallol. Experiments with common oxidizing agents gave results quite different from those obtained with the reducing agents just mentioned. Chlorine-water (saturated solution), bromine-water (saturated solution), potassium chlorate (10 per cent. solution), hydrogen peroxide (saturated solution, fresh), chromic acid (2 per cent. solution), and nitric acid (2 per cent. and 10 per cent. solutions) all yielded negative results when painted on the pancreas. Among the oxidizing agents tried, only nitrobenzol (4 per cent. to 10 per cent. solutions) gave sugar, but a more thorough search would doubtless reveal others which have this effect.

Among substances which have little or no reducing action, but produce glycosuria, may be mentioned sodium salicylate[1] (50 per cent. solutions) and potassium cyanide. On the other hand, sodium thiosulphate (10 per cent. to 90 per cent. solutions), a powerful reducing agent, wholly failed to induce glycosuria.

It is thus clear that we cannot attribute the experimental glycosurias that have been observed merely to the reducing properties of the substances employed, but rather to some obscure toxic action exerted probably on the cells of the pancreas.[2] What we know of the action of potassium cyanide indicates that this toxic action involves interference with intracellular oxidation.

It seemed possible at first, that experimental adrenalin glycosuria might be referable to a temporary inhibition of that function of the

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[1] TABLE SHOWING EFFECT OF APPLYING SODIUM SALICYLATE SOLUTION TO PANCREAS.

Weight of dog.	How applied to pancreas.	Am'nt of soluti'n used.	Strength of solution.	Duration of application.	First catheterization after	Vol. of urine.	Sugar.	Remarks.
12.7 kilo	Painted.	1 c.c.	50 %	15 min.	2 hours.	13 c.c.	2.0 %	
7.7 "	"	2 "	"	25 "	2 "	16 "	3.8 %	
7.7 "	"	1 "	"	15 "	3 "	25 "	0.2 %	
——	Injected.	5 "	"	——	1 h. 50 m.	4½ "	0.3 %	
9.1 kilo.	"	2 "	"	......	2 hours.	12 "	2.8 %	
10.4 "	Painted.	1 "	"	7 min.	1 h. 30 m.	——	9.0 %	Application to tail of pancreas.
5.4 "	"	½ "	"	30 "	2 h. 30 m.	18 c.c.	8.5 %	Application to head of pancreas.

[2] There is no direct evidence that these substances act only on the pancreas, but the cyanide experiments suggest that this may be the case. We hope to have the opportunity to test this question individually with the different poisons that occasion glycosuria.

pancreas which normally prevents the excretion of sugar, but this view soon became untenable for the following reason: If one cuts transversely through the pancreas and duodenum, so that the severed portions of the organ have their only vascular connection through the general circulation, the application of a weak potassium cyanide solution to either portion of the gland is still liable to induce glycosuria. We know from experiments already mentioned that potassium cyanide injected into the circulation failed to cause glycosuria; hence we are justified in assuming that when the cyanide acts on one part of the divided pancreas it has no influence upon the remaining portion, but acts wholly by means of this local action. As it is well known that dogs with one-half the pancreas intact do not develop glycosuria, it is evident that we have in the phenomena of cyanide glycosuria something distinct from the glycosuria that follows extirpation of the pancreas.

When the pancreas is divided in the manner just mentioned the application of a small quantity of adrenalin chloride (1 c.c. of a 1 : 1000 solution) to either end of the gland is generally followed by glycosuria. We know that when adrenalin is injected into the circulation it is capable, unlike dilute solutions of potassium cyanide, of inducing glycosuria; hence this method of experimentation does not enable us to exclude some action of adrenalin upon the unpainted part of the gland and upon other organs, yet the cyanide experiment makes it highly improbable that such action upon the unpainted gland is necessary for the production of glycosuria.

We have at present no indication whether an application of potassium cyanide or adrenalin to the pancreas acts chiefly upon the secreting glandular cells, the cells of the islands of Langerhans, or the nerve endings in the pancreas. As the islands of Langerhans have been shown by Opie to be somewhat more numerous in the tail of the dog's pancreas than in other parts, it was thought desirable to make a series of observations in which the caudal half of the organ was painted with adrenalin, and a second series in which the cephalic and descending half of the gland was so painted. There are fifteen observations in each series. As regards the weights and feeding of the dogs and the operative conditions of the experiments, the two series of observations are comparable. The pancreas was in each case severed into two approximately equal parts, the duodenum being also cut through. The amount of adrenalin chloride solution (1 : 1000) varied from 1 c.c. to 2 c.c., according to the weight of the animal. The time required for the application of the adrenalin solution was usually fifteen or twenty minutes. The urine was collected hourly by catheter for three or four hours after the paintings. Considerable variations in the degree of glycosuria were, as usual, noticeable in different animals. The total excretion of sugar noted in fifteen dogs of the first series, in which the tail half of the pancreas was painted, was 17.25 grammes. The total excretion of sugar by the fifteen dogs of the second series, in which the cephalic half of the gland was painted, was 15.60 grammes. It cannot, of course, be maintained that these results prove the caudal end of the pancreas to be more sensitive to the action of adrenalin than the cephalic half. To determine whether this is actually the case much more numerous observations would have to be made. On the other hand, the results of our experiments are in no way opposed to the possibility that adrenalin exerts its influence through the islands of Langerhans—a possibility which naturally suggests itself, although there is no proof that adrenalin acts exclusively on the pancreas in the production of glycosuria. Some light may perhaps be thrown on this question by a study of the histological conditions in the pancreatic glands of animals that have been treated with intraperitoneal injections of adrenalin through a long period of time.

It has not been possible to induce a permanent glycosuria by means of repeated intraperitoneal injections; but in one dog in which such injections had been made at short intervals during five weeks, with a glycosuria broken only by short intermissions, the islands of Langerhans showed no alterations.

Fatal intraperitoneal doses of adrenalin may set up an acute hemorrhagic pancreatitis in which some of the islands of Langerhans, together with other structures, suffer alteration; but control experiments with intravenous injections indicate that the lesions observed are not necessary to the production of glycosuria.

ON CERTAIN RELATIONS BETWEEN THE ADRENAL GLANDS AND CARBOHYDRATE METABOLISM. The knowledge that extracts of the adrenal gland have the property of inducing glycosuria suggested the inquiry whether the adrenal glands normally possess any influence on carbohydrate metabolism by virtue of their internal secretion. Experiments showed that compression of the adrenal glands is followed by glycosuria; while their exclusion, by extirpation or ligation of their vessels, is followed by a considerable fall in the sugar-content of the blood. These results were confidently interpreted as indicating that the adrenal glands stand in an important relation to carbohydrate metabolism and normally exert a regulatory influence upon the sugar-content of the blood.[1] Unforeseen experimental difficulties have up to the present time made it impossible to prove whether the influence of the adrenals on carbohydrate metabolism is of the nature suggested in the hypothesis that was proposed—that is to say, an influence exerted through the internal secretion of the gland. It is not without interest to review briefly the main facts that have come to light in the course of this study.

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[1] Medical News, October 25, 1902.

On subjecting the adrenal glands of normal dogs (fed on lean meat) to intermittent compression between the thumb and finger glucose quickly appears in the urine. The percentage of sugar may be high (4 or 5 per cent.), but the amount has never been large, and the duration of the glycosuria is not more than a few hours. It is not necessary in order to obtain these results to compress the gland to the point where its structures yield sensibly to the fingers. Control observations on the spleen, in which the organ was much damaged by pressure, failed to show glycosuria. Destructive compression of the pancreas may be followed by the appearance of a small amount of sugar in the urine.

These results were at first interpreted to indicate that the process of compression leads to glycosuria by causing a substance allied to the glycosuria-producing substance of adrenal extracts to enter the blood. It now appears uncertain whether this is the real explanation. In animals the carotids of which were connected with a mercury manometer the adrenal glands were intermittently compressed without giving rise to any increase in the general blood pressure such as one might perhaps expect if the internal secretion of the gland were actually being forced into the circulation in unusual amount. This observation, together with the fact that compression of the pancreas may occasion glycosuria, makes it necessary to admit that nervous influences may be largely responsible for the sugar which appears after compressing the adrenals. Nevertheless, the fact that compression of a single adrenal gland may occasion pronounced glycosuria suggests that functional disturbances in this gland readily bring on at least a temporary glycosuria.

Numerous experiments have been made in which the adrenal vessels were either ligatured or in which the adrenal glands were extirpated bilaterally. In most of these observations the blood sugar-content before operation was compared with the blood sugar-content about four hours after operation. A considerable fall in the percentage of blood sugar was found in almost all instances. Controls show that this fall cannot be accounted for either by the slight lengthening of the fasting period or by the small amount of blood (8 to 25 grammes) abstracted for the determination of the blood sugar.

In a few instances the blood sugar after operation on the adrenals has been somewhat increased after the lapse of four hours. There is good reason to think that etherization usually increases somewhat the sugar-content of the blood, and it is likely that our exceptional results can be accounted for by the action of this anæsthetic. The fact that we do not know any narcotic or anæsthetic which does not in itself affect the sugar-content of the blood is still an obstacle to the correct

TABLE ILLUSTRATING THE FAILURE OF ADRENALIN TO INDUCE GLYCOSURIA.

Weight of dog.	Nature of diet, etc.	Nature of operation on adrenals.	Interval between operation and injection of adrenalin.	Dose of adrenalin.	Mode of administration.	Catheterization following adrenalin after	Volume of urine.	Sugar.	Remarks.
6.9 kilo.	Lean meat.	Adrenal vessels ligatured.	3 h. 25 min.	5 c.c. (1-1000)	Intraperitoneal	1 hour. 2 hours. 3 " 4 "	5 c.c. 4 " 8 " 18 "	Trace. Negative. Trace. Negative.	A second injection of 9 c.c. adrenalin (1-1000) on following day, quite negative as regards sugar.
6.8 kilo.	Unknown; well nourished; lacteals full.	Adrenal vessels ligatured.	4 h. 40 min.	5 c.c.	Intraperitoneal	1 hour. 2 hours. 3½ "	5 c.c. 4 " 12 "	Negative. " "	No fluid in peritoneal cavity.
9.1 kilo.	Lean meat.	Right adrenal vessels tied; left gland removed.	4 h. 15 min.	7.5 c.c.	Intraperitoneal	1 hour. 2 hours. 3½ "	10 c.c. 4 " 9 "	Negative. " "	No fluid in peritoneal cavity.
8.7 kilo.	Lean meat, starved 60 hours.	Adrenal vessels ligatured.	4 h. 35 min.	8 c.c.	Intraperitoneal	36 min.	4 c.c.	Trace.	A subsequent injection of one sheep's gland (dried) caused the appearance of 0.5-1 per cent. reducing substance in 200 c.c. urine.
15.6 kilo.	Starved 40 hours; well nourished.	Adrenal vessels ligatured.	4 h. 20 min.	8 c.c.	Intraperitoneal	1 hour. 2 hours. 4 " 17 "	5 c.c. 12 " 40 "	Negative. Trace. Slight trace. Negative.	No fluid in peritoneal cavity.
7.7 kilo.	Starved 40 hours; fairly well nourished.	Adrenals removed.	4 hours.	5 c.c.	Intraperitoneal	1 hour. 4 hours.	8 c.c. 5 "	Slight trace. " "	No fluid in peritoneal cavity.
8.2 kilo.	Unknown; well nourished.	Adrenals removed.	3 h. 50 min.	4 c.c.	Intraperitoneal	1 hour.	8 c.c.	Negative.	
15.9 kilo.	Starved 40 hours; well nourished.	Adrenals removed.	5 hours.	8 c.c.	Intraperitoneal	1 hour. 3 hours.	10 c.c. 35 "	Negative. "	

interpretation of our results. Whether the fall in blood sugar which we have noted after the above-mentioned operations on the adrenals can be attributed wholly or in part to the exclusion of the internal secretion of these glands is not yet clear.

It is a fact of considerable interest that under certain conditions the injection of adrenalin into the peritoneal cavity failed to bring on glycosuria after the adrenal vessels had been ligatured or the adrenal glands had been extirpated. This result is the more striking because of the great regularity with which intraperitoneal injections of adrenalin induce marked glycosuria in normal dogs. If the injection of adrenalin be made within two hours of the operation on the adrenal glands glycosuria usually appears, but in every instance where the injection was not given until the lapse of four hours or a longer period sugar either did not appear in the urine or appeared in mere traces. The table on page 57 makes this point clear.

The necessity for control observations is, of course, obvious, and the following experiments are of interest in this connection:

Experiment 1. Dog; weight, 7 kilos. Poorly nourished; not fed for twenty-four hours. The mesenteric vessels passing to and from a loop of jejunum six inches in length were ligated with two ligatures, and the loop itself was tied off. No ether used. Four hours after this operation 4 c.c. adrenalin chloride solution (1 : 1000) were injected into the peritoneal cavity; 8 c.c. of urine collected one hour later showed 6.2 per cent. sugar.

Experiment 2. Dog; weight, 18 kilos. Well nourished; twenty-four hours' fast. Etherized and vessels and nerves of the spleen ligatured about one and a half inches from the spleen, numerous ligatures being employed. First hour after operation 35 c.c. urine, about 0.5 per cent. sugar; second hour after operation 10 c.c. urine, about 0.3 per cent. sugar; third hour after operation 11 c.c. urine, slight reduction; fourth hour after operation 13 c.c. urine, negative or slight trace. After four hours animal received 8 c.c. adrenalin chloride solution (1 : 1000) in the peritoneal cavity. Fifty-five minutes later 49 c.c. urine, 2.8 per cent. sugar; two hours and a half later 40 c.c. urine, 6.1 per cent. sugar.

Experiment 3. Dog; weight, 11 kilos. Well nourished; not fed for twenty-four hours. Etherized and splenic vessels and nerves tied off with numerous ligatures, as in Experiment 2. First hour after operation 14 c.c. urine gave 0.44 per cent. sugar; second hour after operation 14 c.c. urine gave a slight reduction; third hour after operation 18 c.c. urine gave a slight reduction; four and a quarter hours after operation 18 c.c. urine gave a trace of reduction. After four and a quarter hours animal received 5 c.c. adrenalin in the peritoneal cavity. Fifty minutes later 23 c.c. urine gave 1.78 per cent. sugar; two and a half hours later 35 c.c. urine gave 4.9 per cent. sugar.

These and similar control experiments show that operations on the spleen or intestine do not lead to an abolition of the property of adrenalin to induce glycosuria when put into the peritoneal cavity. It occurs to one that the operation of ligating the adrenal vessels or extirpating the glands may be followed by a disturbance of absorption from the peritoneum; but if this be the case it is difficult to see why it should not also follow operations on the spleen. It also occurs to one that the injected adrenalin may have been mixed with blood, and thus rendered less active; but hemorrhage did not occur in any case, and the peritoneal cavity was in several instances practically free from fluid. The failure of adrenalin to cause glycosuria in our experiments seems to point to some special influence connected with the exclusion of the adrenals; but whether the real explanation lies in the elimination of the adrenal internal secretion, or in some obscure nervous disturbance, it has not been possible to determine. It is not certain that the adrenalin used in these experiments is equivalent to the internal secretion of the dog's adrenals.

In five dogs from which the pancreas was totally removed after bilateral ligation of the adrenal vessels it was observed that the urine subsequently passed either contained no sugar or only a small quantity.

In those cases where the urine contained some sugar this disappeared before the lapse of many hours. Comparing these results with those which we have obtained from numerous extirpations of the pancreas alone, there seems to be no doubt that exclusion of the adrenal glands modifies the onset of pancreatic glycosuria in the direction of greatly reducing the early excretion of sugar.[1] Even in cases where the

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[1] Experiments 1, 2, and 3 illustrate the inhibition of pancreatic glycosuria after operations on the suprarenals. A similar inhibition was not observed after ligature of splenic vessels. Controls involving operations on the nervous system only have not been made.

Experiment 1. Dog; weight, 10 kilos. Bladder emptied; urine normal. Suprarenal vessels ligatured on both sides. Immediately afterward pancreas completely extirpated.

One hour 15 minutes after pancreatic extirpation, 2¼ c.c. urine contained no sugar.

Two hours 30 minutes after operation, 6 c.c. urine contained about 0.3 per cent. sugar.

Three hours 30 minutes after operation, 12 c.c. urine with 10 c.c. Fehling's solution gave slight greenish reduction.

Four hours 30 minutes after operation, 8 c.c. urine, negative for sugar.

Experiment 2. Dog; weight, 10.9 kilos. Bladder emptied; urine normal. Suprarenal vessels ligatured on both sides; 27 minutes later pancreas had been completely extirpated.

One hour after operation, 5 c.c. urine contained about 0.5 per cent. sugar.

Two hours after operation, 4 c.c. urine contained about 0.4–0.5 per cent. sugar.

Three hours after operation, 1.5 c.c. urine contained 0.3–0.4 per cent. sugar.

Four hours thirty minutes after operation, 4–5 c.c. bloody urine contained no sugar.

Experiment 3. Dog; weight, 9.1 kilos. Bladder emptied, urine normal. Suprarenal vessels ligatured on both sides. Twenty-five minutes after completion of these operations the pancreas had been completely extirpated.

One hour 45 minutes after last operation, 6 c.c. urine contained not more than 0.2 per cent. sugar.

Three hours 45 minutes after last operation, 9 c.c. urine gave very slight reduction.

Five hours 45 minutes after last operation, 10 c.c. urine, quite negative.

Ten hours after last operation, 9 c.c. urine, quite negative.

Experiment 4. Dog; weight, 9.2 kilos. Bladder emptied, urine normal, pancreas completely extirpated. One hour later 10 c.c. urine contained 7 per cent. sugar. One hour and adrenal operation follows extirpation of the pancreas a high grade of glycosuria may be rapidly lessened; but ultimately the excretion of sugar again reaches a high level, so that the adrenal influence, whatever it may be, is a transient one. In the interpretation of these results one has to bear in mind that the glycosuria of simple pancreatic extirpation may show for a time a spontaneous falling off in the quantity of sugar excreted. It seems to us probable that a severe form of shock may be responsible for the inhibition of pancreatic glycosuria that has been observed.

Although the experimental results that have been here described point to a closer relationship between the adrenal glands and carbo-

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15 minutes after pancreatic extirpation right adrenal vessels were tied; 8 minutes later left adrenal vessels were tied. Urine collected 12 minutes later contained 6.5 per cent. sugar.

One hour after ligation of adrenals, 6 c.c. urine contained 5.6 per cent. sugar.

Four hours after ligation, 20 c.c. urine contained 4.6 per cent. sugar.

Eight hours after ligation, 20 c.c. urine contained 0.6 per cent. sugar.

Soon after suppression of urine occurred.

Experiment 5. Dog; weight, 16.8 kilos. Bladder emptied, urine normal, pancreas completely extirpated. Twenty minutes later right adrenal vessels tied. Urine obtained by catheter showed slight reduction. One hour after operation on left adrenal, 5 c.c. urine contained 6 7 per cent. sugar. Ten minutes later left adrenal vessels tied.

1 hour 15 minutes	after ligation of	left adrenal	vessels,	13 c.c.	urine contained	4.5	p. c.	sugar.
2 hours 15 minutes	"	"	"	17 c.c.	"	1.6	"	"
3 hours 15 minutes	"	"	"	40 c.c.	"	0.2	"	"
4 hours 15 minutes	"	"	"	16 c.c.	"	0.3	"	"
5 hours 15 minutes	"	"	"	27 c.c.	"	1.25	"	"
6 hours 15 minutes	"	"	"	13 c.c.	"	1.75	"	"
7 hours 15 minutes	"	"	"	4.5 c.c.	"	2.25	"	"
8 hours 15 minutes	"	"	"	8 c.c.	"	2.25	"	"

Soon after this suppression set in.

Experiment 6. Dog; weight, 8.7 kilos; starved 60 hours. Bladder emptied, urine normal, pancreas completely extirpated. Urine immediately after contained no sugar. Twenty-seven minutes after extirpation adrenal vessels tied on both sides. Urine immediately after contained no sugar.

1 hour	after ligation of	adrenal vessels,	6 c.c.	urine contained	0.1–0.2	per cent.	sugar.
3 hours	"	"	5 c.c.	"	a trace of sugar.		
4 hours	"	"		"	"	"	
9 hours	"	"	34 c.c.	"	"	"	
23 hours	"	"	12 c.c.	"	2.2	per cent.	sugar.
28 hours	"	"	5 c.c.	"	5.0	"	"
29 hours	"	"	10 c.c.	"	5.5	"	"
32 hours	"	"	17 c.c.	"	5.0	"	"

Experiment 7. Dog; weight, 7.7 kilos; not fed for 30 hours before operation. Bladder emptied, urine normal; pancreas totally extirpated at 4.05 P.M.; aseptic operation.

2 hours	after operation,	4 c.c.	urine contained	7	per cent.	sugar.
5 hours	"	45 c.c.	"	8	"	"
19 hours	"	140 c.c.	"	9	"	"
23 hours	"	35 c.c.	"	14.3	"	"

On the following day, 23 hours after the pancreatic extirpation, the adrenal vessels were ligated on both sides.

1 hour	after ligating	adrenal vessels,	11 c.c.	urine contained	6.25	per cent.	sugar.
2 hours	"	"	13 c.c.	"	6.5	"	"
3 hours	"	"	13 c.c.	"	6.5	"	"
7 hours	"	"	26 c.c.	"	5	"	"

Subsequent collections were impracticable, although the animal lived nearly 24 hours longer.

hydrate metabolism than has been previously recognized, it cannot be maintained that we have as yet succeeded in obtaining unequivocal evidence that the phenomena described are due to the excessive influence of the adrenal internal secretion or to the exclusion of this secretion from the circulation. Some of these phenomena can probably be equally well accounted for on the supposition that imperfectly understood nervous factors have been brought into play. It must, therefore, be left to further experiments, in which close attention is given to control observations on the nervous system, to determine whether the internal secretion hypothesis is tenable.

A REPORT OF TWO CASES OF MULTIPLE SCLEROSIS, WITH NECROPSY:

WITH REMARKS ON MUSCULAR ATROPHY, SECONDARY DEGENERATION, AND LOSS OF TENDON REFLEXES, WITH INCREASED MUSCULAR TONICITY, OCCURRING IN THIS DISEASE.[1]

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Multiple sclerosis seems to be a rare disease in America, and scarcely any cases with necropsy are to be found in the literature of this country. I am inclined to think that some cases are overlooked, and that the disease, while uncommon, does occur more frequently than the paucity of records gives us reasons to believe. B. Sachs remarked at the time he wrote his critical digest on multiple sclerosis, in 1898, that he had been able to find only one necropsy record of a case of this disease published in America, and that was by Seguin, and was incomplete.

Since the publication of Sachs'[2] paper a case with necropsy has been reported by Burr and McCarthy[3] (1900), and another that probably should be classed under multiple sclerosis, although published only in abstract, May, 1902, by J. R. Hunt.[4] The paper by E. W. Taylor[5] is one of the best on the subject by American writers, but the cases he reports occurred in Germany, and are a contribution to German literature.

I report two cases, with microscopic examination of the nervous tissues. The first case was in the service of Dr. F. X. Dercum, at the

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[1] Read in abstract at the annual meeting of the American Neurological Association, June 1902.

[2] Sachs. Journal of Nervous and Mental Disease, 1898.

[3] Burr and McCarthy. Ibid., 1900.

[4] J. R. Hunt. Ibid., May 12, 1902, p. 288.

[5] E. W. Taylor. Deutsche Zeitschrift für Nervenheilkunde, vol. v.